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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 08/803,702
Filing Date: February 21, 1997
Appellant(s): MAINO ET AL.



Douglas A. Petry, Ph.D.
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 1/24/05 appealing from the Office action mailed 4/28/04.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the

structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because the Summary does not accurately indicate the proper page and line numbers wherein support for the claimed method can be found. For example, Appellant cites page 5, lines 15-17 in support of the second step of Claim 19. Yet a review of the cite discloses the addition of an inhibitor of cytokine secretion during a specific 4 hour activation period, whereas the claimed step is much broader in scope reciting no such time limitation.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

ELKELES, A., et al. FEMS Microbiol. Lett. 1994;116:221-224.

ROBIN, P., et al. Eur. J. Cell Biol. July, 1995;67:227-237.

O'NEILL-ANDERSEN, N.J., et al. Clin. Diag. Lab. Immunol. 2002;9(2):243-250.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

**I.** Claims 19-24, 26-33, 35-38, 40-55, and 61-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of "an inhibitor of cytokine secretion" (Claim 19), other than Brefeldin A (BFA). The specification discloses no definition for said inhibitor and teaches only the single species, BFA. Absent any definition, the claim must be read broadly to include any chemical that could inhibit cytokine secretion, presumably including toxins ranging from benzene to sodium azide. Thus, the specification fails to adequately define the claimed invention and one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

**II.** Claims 19-24, 26-33, 35-55, and 61-65 are rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is not enabling. Elements critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure.

At page 4, the specification discloses, "At its simplest, the methodology involves a step process, which involves culturing with the antigen specific stimulus and analyzing an aliquot of the cultured sample for expression of one or more intracellular cytokines and/or early activation antigens in combination with one or more T-cell markers." Clearly then, *at its simplest*, the specification discloses that the claimed method requires *in vitro* antigen stimulation and culture; note that the culture step is not a claimed limitation. Further note that it is well-established that antigen stimulation in the absence of costimulation will result in anergy (not activation), thus costimulation (as recited in Claim 20) must comprise a limitation of independent Claim 19. Example 4 discloses additional required steps. For example, it is disclosed that a maximal response depended critically on the method being performed in slant tubes due to the geometry of the T cell/accessory cell interaction. The Example also discloses that the detection method of the instant claims also depended on "the inclusion of CD69 (not just any activation marker) assessment in the multiparameter protocol." Additionally, the Example discloses that the analysis "requires" the collection of at least 50,000 events. Most importantly, the specification and the post-filing art disclose/teach that the inclusion of an inhibitor of cytokine secretion is essential to the success of the claimed assay. Note that the inhibitor of cytokine secretion, BFA is used in all of the examples in the specification. Further note that, while BFA and monensin might be considered related, post-filing teachings indicate that in assays similar to those encompassed by the instant claims, the effects of the inhibitors are not identical, and the inhibitors

should not be considered interchangeable. See for example, O'Neill-Andersen et al. wherein functional differences between monensin and BFA are examined. Note that the reference teaches, "A key aspect of intracellular cytokine detection is trapping the cytokine within the cell," and "We conclude that the choice of a protein transport inhibitor is an important variable in this assay." Thus, it would appear that these investigators did not find inhibitors of cytokine release to be "auxiliary to the invention" (as argued by Applicant), nor did they find it "unimportant which inhibitor is used to inhibit cytokine secretion, so long as cytokine secretion is inhibited," (also argued by Applicant).

**(10) Response to Argument**

Ground I - inadequate written description:

> Appellant presents two arguments, first:
> "The use of an inhibitor of cytokine secretion to allow intracellular cytokines to accumulate, thereby facilitating the detection of the intracellular cytokines, was known at the time of the invention. The description need only describe in detail that which is new or not conventional", and second,
> "The claims, read as a whole, are drawn to a new use of known compounds (an inhibitor of cytokine secretion) and are not drawn to either novel compounds per se or to methods using novel compounds. In such a case, the applicant is not required to discover all the compounds from this class that would be useable in the methods".

Regarding the use of an inhibitor of cytokine secretion, Appellant further cites Jung et al., Elson et al., Prussin et al. Picker et al., and B-D Application notes as the closest prior art of record. Additionally, Appellant repeatedly cites *In re Futterer*.

It remains the Examiner's position that Appellant has selectively picked references which suit Appellant's case while ignoring others. For example, in the Office action of 12/02/02 the Examiner cited Elkeles et al. (1994) as well as Robin et al. (1995) for teaching that many other chemicals including azide and nicodazole *might* be considered to be inhibitors of protein secretion. In the response of 9/03/03 (and similarly again here in the instant arguments) Appellant stated, "Furthermore, if others in the future discover another suitable inhibitor of cytokine secretion, the present claims should not be so restricted that they can be avoided merely by using some inhibitor of cytokine secretion not described in the specification". Note the "suitable inhibitor" in Appellant's argument. Clearly there are countless chemicals that can stop cytokine secretion merely by killing the cell or inhibiting proliferation, e.g., chloroquine, cytochalasin, bafilomycin, or vincristine, etc. But Appellant's argument makes it clear that even Appellant does not know whether all such protein secretion inhibitors would prove "suitable" in the claimed method. And this property in particular is what separates the fact pattern in this case from that in *In re Futterer*.

Accordingly, Appellant's argument that the instant method comprises merely a new use of known compounds has not been found to be persuasive by the Examiner. Appellant has described a critical component in the claimed method by function only. No common structure is disclosed. And regarding the disclosure of a representative number of species, just one, BFA, is disclosed.

Ground II - lack of enablement:

Appellant appears to be confused as regards the elements of the instant rejection. As set forth in the Final Office action of 4/28/04, the rejection of record was first made in the Non-final Office action of 12/02/02. That the entire prosecution history has not been reiterated in each intervening Office action does not obfuscate the fact that it is the rejection of 12/02/02,as set forth above, that is at issue here.

Appellant argues that various combinations of the individual steps set forth as required in the claimed method have been added piecemeal to various claims at various times during the course of prosecution.

It has always been the Examiner's position that only a claim, e.g., Claim 66, reciting *all* of the minimal steps is enabled. It remains the Examiner's position that Appellant, not the Examiner, wrote the specification. Appellant, not the Examiner chose to use the words, "At its simplest" (in describing the minimal requirements of culturing with the antigen specific stimulus and analyzing an aliquot of the cultured sample for expression of one or more intracellular cytokines and/or early activation antigens in combination with one or more T-cell markers at page 4), "critical" (in describing the necessity of employing slant tubes at page 16), and "required" (in describing the minimum number of events to be measured at page 17). Other required elements, such as the use of costimulation for the activation of T cells, result from the most minimal requirements fundamental to basic immunology.

In summing up Appellant's review of relevant case law, Appellant concludes:

> "In summary, a rejection based omission of a critical element is improper unless the specification, taken as a whole, teaches that omission of the element would result in the invention being wholly inoperable. Elements that represent preferred embodiments, e.g., elements that optimize, maximize, or increase accuracy of the results, or elements that set for the practical limits of operation are not critical".

It remains the Examiner's position that the elements set forth in the rejection are indeed critical and cannot be considered to be simply preferred embodiments.

Appellant argues that the limitation reciting the use of an inhibitor of cytokine secretion is no longer an issue as the limitation has been added to the claims.

As set forth in the rejection, and not addressed here by Appellant, not all inhibitors of cytokine secretion function identically, see O'Neill-Andersen et al. (2002). Note too that in response to the rejection for inadequate written description Appellant stated that the use of "suitable" inhibitors of cytokine secretion are encompassed by the instant claims (see for example the instant Brief, page 18, 4$^{th}$ to last line). Thus, Appellant is admitting that not all inhibitors of cytokine secretion would function in the claimed method yet no method for selecting "suitable" inhibitors of cytokine secretion has been disclosed.

Appellant argues that the use of slant tubes comprises only a preferred embodiment of the claimed method. Appellant cites the disclosure at page 16, "First, the geometry of the T

cell/accessory cell interaction was critical for Ag responses; maximal responses were observed in slant tubes that allowed close proximity of T cells and accessory cells, but still allowed adequate media access to responding cells".

It is the Examiner's position that the cited section discloses that the geometry of cell interaction is critical and that the only disclosed geometry is provided by slant tubes, thus, the use of slant tubes is critical.

Appellant cites Suni et al. (1998) and argues that post-filing evidence is acceptable.

It remains the Examiner's position that an invention must be enabled at the time of filing. Post-filing evidence is acceptable to demonstrate that an aspect of an invention as set forth in the specification was indeed enabled at the time of filing. Such is not the case in this instance. At the time of filing the specification disclosed that the geometry provided by slant tubes was critical. Post-filing evidence cannot change this disclosure. Further, in considering the teachings of the reference it must be noted that the method of the reference is not the over-simplified method of the instant claims. First note that the reference teaches the use of slant tubes for incubation (page 94, column 2), thus it is unclear why Appellant would cite the reference in support of *not* using slant tubes. Also note the use of a costimulatory αCD28 monoclonal antibody. Then note that the method teaches the absence of BFA for the first hour of incubation, "to enable antigen processing by antigen presenting cells" (page 90, column 2). Finally note that the reference also

teaches a 15 minute incubation at room temperature after EDTA addition, *a step that is found nowhere in the instant specification.*

Appellant argues that the collection of 50,000 events comprises only a preferred embodiment of the claimed invention. Appellant cites the disclosure at page 16-17, "Finally, because of the relatively small size of the Ag-specific populations, accurate assessment of these responses required the routine collection and analysis of at least 50,000 events per determination".

It is the Examiner's position that the cite speaks for itself; the claimed method *requires* the collection and analysis of at least 50,000 events.

Appellant cites Example 3 as disclosing the collection of only 48,000 events.

It is unclear why Appellant would cite Example 3, which does not disclose the analysis of an antigen-specific response, indeed, the "Example" discloses no actual experiment at all.

Appellant again cites Suni et al. (1998) and argues that post-filing evidence is acceptable.

See the Examiner's position on Suni et al. (1998) set forth above.

Appellant argues that Claim 39 recites the use of BFA as does independent Claim 64.

It is the Examiner's position that neither claim recites the minimum number of events to be collected, nor the use of slant tubes, nor the inclusion of a costimulatory molecule such as an αCD28 monoclonal antibody.

Appellant argues that independent Claim 64 recites the use of BFA and slant tubes.

It is the Examiner's position that the claim fails to recite the minimum number of events to be collected nor the inclusion of a costimulatory molecule such as an αCD28 monoclonal antibody.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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5/25/01

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